

Art Unit 1812

Paper No. 13

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Appeal No. 92-3627

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ON BRIEF

PAT. & T.M. OFFICE  
BOARD OF PATENT APPEALS  
AND INTERFERENCES

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* Thomas F. Deuel  
Yue-Sheng Li  
Ned R. Siegel  
and  
Peter G. Milner

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Application for Patent filed June 21, 1990, Serial No. 07/542,232; which is a continuation-in-part of application Serial No. 07/462,156, filed January 8, 1990, now abandoned. Heparin-Binding Growth Factor.

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Scott J. Meyer et al. for Appellants.

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Supervisory Patent Examiner - David L. Lacey  
Examiner - Shelly J. Guest

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Before Goldstein, Goolkasian and W. Smith, Administrative Patent Judges.<sup>1</sup>

Goolkasian, Administrative Patent Judge.

Appellants' invention relates to proteins known as heparin-binding growth factors (HBGF) and to nucleic acid molecules (DNA) which code for the proteins. Claims 1 through 3,

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<sup>1</sup>The Commissioner of Patents and Trademarks has authorized the Examiners-in-Chief of the Board of Patent Appeals and Interferences to use the title of Administrative Patent Judge.

which relate to the proteins, were withdrawn from examination pursuant to a requirement for restriction. Claims 4 through 7, which are directed to purified and isolated DNA sequences encoding the heparin binding growth factors, stand before us.

Appellants urge that claims 4 and 5 be considered separately from claims 6 and 7. The former are directed to DNA sequences which code for the human form of the protein whereas the latter are directed to DNA sequences which code for the bovine form of the protein. Although both the human and bovine species are mammalian, the amino acid sequences of the respective proteins have slightly different structures and are coded for by slightly different DNAs.

Claim 4 is directed to the DNAs which code for the human version of the protein. It sets forth the amino acid sequence of the protein. It is illustrative of the invention and is appended hereto.

The references relied on by the examiner are:

Bohlen et al. (Bohlen) (European  
Patent Application)

0326075

Aug. 2, 1989

Rauvala, *The Embo Journal*, "An 18-kd heparin-binding protein of developing brain that is distinct from fibroblast growth factors," Vol. 8, No. 10, 1989, pages 2933-2941.

Maniatis, *Molecular Cloning: A Laboratory Manual*, "Screening Bacteriophage  $\lambda$  Libraries for Specific DNA Sequences by Recombination in *Escherichia coli*," Cold Spring Harbor Laboratory, New York, 1982, pages 353-361.

All of appellants' claims stand rejected under 35 U.S.C. § 103 over Bohlen or Rauvala in view of Maniatis.<sup>2</sup> Both the Bohlen and Rauvala references describe the isolation and purification of an 18 kd heparin-binding protein. Both references provide accurate, but partial, information regarding the amino acid sequence of the protein. Specifically, both references provide the amino acid sequence of the N-terminal portion of the protein. Neither reference discusses the DNA which codes for the protein and neither reference teaches isolation of the DNA. The Maniatis reference, a textbook, teaches a general method of isolating the DNA sequence of a gene which codes for a protein by screening a DNA library using an oligonucleotide probe wherein the nucleotide sequence selected for the probe is based on the N-terminal amino acid sequence of the protein.<sup>3</sup> The Maniatis reference may be fairly said to teach "a general method of probing" to isolate DNA corresponding to the protein of interest when the N-terminal amino acid sequence of the protein is known.

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<sup>2</sup>There are two separate rejections before us; Bohlen in view of Maniatis, and Rauvala in view of Maniatis. The Bohlen reference teachings are more comprehensive than those of Rauvala.

<sup>3</sup>A discussion of probe design and use of probes to isolate DNA can be found in *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207, 1208, 18 USPQ2d 1016, 1022 (Fed. Cir. 1991).

It is the examiner's position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to clone the gene for HBGF using the technique of Maniatis.

The tenor of appellants' arguments is that the examiner has focussed on the obviousness of the process of making the HBGF DNAs, despite the fact that it is products (genes) that are claimed in the application, not processes.<sup>4</sup> Specifically, appellants note that the primary references, Bohlen and Rauvala, do not mention DNA or suggest isolation of DNA and that the Maniatis reference is nothing more than a state-of-the-art treatise on the principles and techniques of gene cloning. Appellants also note that none of the claims herein relate to the "method of gene cloning" (Brief, page 7) but, rather, relate to novel and unobvious DNA compounds. Appellants urge that the invention herein is directed to chemical compounds (nucleotides) which have certain structural characteristics and that in order for a reference to be a valid reference against the compounds claimed, the reference must likewise disclose a teaching of the structure of the claimed chemical compound or compounds homologous thereto, and not merely methods or techniques for

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<sup>4</sup> We have intentionally paraphrased footnote 3 of *Amgen Inc. v. Chugai Pharmaceutical Co.*, *supra*, 927 F.2d at 1207, 18 USPQ2d at 1022.

making the chemical compounds (Brief, page 8). Appellants point out that Maniatis, the only reference which relates to gene cloning, is specifically directed to the cloning of a different DNA which has no homology with the claimed DNA. Appellants argue that the examiner has completely confused the instant issue of patentability of novel chemical compounds under § 103 with the issue of patentability of a method of isolating chemical compounds which is a "non-issue" because the claims do not relate to methods.

What is at issue, then, is whether or not knowledge of the partial amino acid sequence of a protein, in conjunction with a reference indicating a general method of cloning, renders the invention as a whole, i.e., the gene, *prima facie* obvious.

This issue is of importance because the isolation and sequencing of a protein involves different technology and equipment than is used in the isolation and sequencing of DNA. When those skilled in the art publish the sequence of a useful protein, that information, indeed the protein itself, may well be dedicated to the public. However, when the protein of interest is a less-abundant protein it cannot readily be produced in quantity and at reasonable cost by isolating the protein from tissue sources. In order to economically produce a less-abundant protein in quantity, it is a necessary and usual practice to isolate the DNA so as to clone the DNA into a host organism and

have the organism produce the protein of interest via its metabolic processes. When a patent issues on the DNA which codes for the protein, the patent owner receives the exclusive right to the DNA and, practically speaking, to the preparation of commercial quantities of the protein which requires the DNA for its production.<sup>5</sup> This is true whether or not isolation of the DNA is accomplished via routine or extraordinary techniques.

We are constantly advised by the patent examiners, who are highly skilled in this art, "that cloning procedures are routine in the art." The textbooks available to this Board indicate that there are several alternative techniques useful for cloning genes. One text, Watson et al., Recombinant DNA-A Short Course, Scientific American Books, 1983, describes screening of a phage library as follows:

Screening a mere million phage plaques will effectively sample all the DNA of the mammalian cell for a given gene. Thus, for a specific cDNA probe, at worst, only a few weeks may be necessary to screen a phage  $\lambda$  library for the respective genes. (page 78, copy attached)

In other words, the examiners urge that when the sequence of a protein is placed into the public domain, the gene is also placed into the public domain because of the routine nature of cloning techniques. We surmise that it is this

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<sup>5</sup>Appellants' claims cover all possible DNA sequences which code for the proteins of interest.

reasoning that caused the parties and District Court in *Amgen v. Chugai Pharmaceutical Co.*, 13 USPQ2d 1737 (D.Mass. 1989), to focus on the method of isolating the gene rather than on the chemical nature of the claimed gene product.

#### ***FACTUAL FINDINGS***

We agree with appellants that the Bohlen reference does not, of itself, suggest the chemical structure of the DNA which codes for the heparin-binding protein. However, the Bohlen reference has other very valuable and germane teachings therein. Bohlen describes a group of proteinaceous growth factors, designated heparin-binding brain mitogens (HBBMs). Bohlen notes the following about the proteins. The proteins have defined molecular weights, one protein having a molecular weight of 18kd. The proteins possess a specific 19 amino acid N-terminal sequence which differs from that of other known proteins. HBBMs having the same N-terminal sequence and the same type of mitogenic activity have been found in both bovine and human brain tissue. Rats and chicken brains are also said to contain HBBMs (Bohlen, page 1, lines 5-20). Bohlen specifically notes that the identity of the N-terminal sequences among the various sources of HBBMs suggests that the sequence is conserved as a result of evolutionary pressure and that there is a likelihood that the proteins are highly homologous between species (page 5, lines

26-30). Indeed, Bohlen found the N-terminal sequences of all three HBBMs to be identical to each other for the first 19 amino acids with the human HBBMs possessing the same N-terminal sequence as bovine HBBMs (page 8, lines 1-5). Bohlen indicates the HBBMs are brain-specific (page 5, line 35).

The Rauvala reference is similar to Bohlen in its teachings but deals primarily with proteins extracted from rat brain. Rauvala indicates that he isolated the protein and determined that the amino terminal sequence contained seven lysine residues. Rauvala sets forth an accurate sequence for the first 14 amino acids. Rauvala does not contain information regarding homology amongst species but, like Bohlen, suggests that the protein is brain-specific. On this point Rauvala specifically states that the protein was not found in tissues other than brain (page 2934, column 2, and Figure 5).

The Maniatis reference is a state-of-the-art teaching of a technique useful for screening libraries of bacteriophage  $\lambda$  recombinants for specific DNA sequences. The reference describes a method of probing whereby a restriction fragment containing a probe sequence is cloned into a plasmid and the hybrid plasmid is used to transform cells. A population of the transformed cells is then infected with a library of bacteriophage  $\lambda$  recombinants that carry mammalian DNA fragments. Upon contact, recombination occurs when the mammalian DNA sequence of the probe cloned into

the plasmid is homologous to the sequence cloned into the infecting bacteriophage. Figure 10.5 on page 355 of the reference explains the general process.

*OPINION*

We consider first the rejection over Bohlen in view of Maniatis.

35 U.S.C. § 103 precludes the grant of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. The Bohlen reference advises those of ordinary skill in the art about the existence of a novel protein growth factor said to be useful in wound healing, bone healing, etc. The reference teaches that the bovine protein has a specific sequence of 19 amino acids at the N-terminal. The reference also teaches that the sequence is highly conserved from species to species, i.e., human, bovine and rat.

One of ordinary skill in this art, advised of the existence and isolation of a functional protein, is also necessarily advised of the existence of a gene which codes for

the protein, but does not know the gene's structure.<sup>6</sup> There is incentive or motivation to isolate (clone) the gene for any functional and useful protein because it would then enable production of large amounts of the protein for further study and commercial use.

We do not subscribe to appellants' proposition that the failure of the references to teach the structure of the claimed DNA precludes the teachings thereof from serving as evidence to establish a *prima facie* case of obviousness. The argument is contrary to a body of law which holds that a product may be described by the process of making it. *See In re Pilkington*, 411 F.2d 1345, 162 USPQ 145 (CCPA 1969); *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Indeed, the Federal Circuit has recognized that a gene, being a chemical compound, could be defined "by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguished it [from other materials]." *See Amgen, supra*, 927 F.2d at 1206, 18 USPQ2d at 1021; *Fiers v. Sugano*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993).

As noted in *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966), the particular structure or form of a chemical

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<sup>6</sup> The relationship between a gene (DNA) and the protein (amino acids) coded for by the gene is discussed at footnote 4 of *Amgen, supra*.

compound is an important consideration in determining obviousness under 35 U.S.C. § 103. But it is not the only consideration. A compound may well be defined or described by characteristics other than its chemical structure.

Though those skilled in the art may be unaware of the exact chemical structure of a gene they are aware that it is composed of an unknown but established, relatively unchanging array of nucleotides which code for the particular protein. Importantly, they are also aware that the gene will hybridize with another DNA having the same assemblage of adjacent nucleotides for at least a portion of the gene. Those skilled in the art are also aware of established procedures for isolating the gene using the hybridization phenomenon. One such procedure, a probing technique, is taught in the Maniatis reference cited by the examiner. We agree with the examiner that the Bohlen reference would have suggested to those of ordinary skill in this art that they should make<sup>7</sup> the gene, and the Maniatis reference would have taught a technique for "making" the gene with a reasonable expectation of success. Accordingly, we affirm the examiner's rejection.

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<sup>7</sup> In this art, most genes are so large that they are not "made from scratch", i.e., by reacting standard chemicals. Rather, they are premade by the body (genomic genes) or by genetic engineering (cDNA) and cloned from large "libraries" to isolate the gene.

We recognize that this case is somewhat similar to that before the Federal Circuit in *In re Bell*, 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993). The *Bell* case is readily distinguished.

In *Bell*, the Court described the issue before them as follows:

The issue before us is whether the Board correctly determined that the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning renders the genes prima facie obvious.

Although the Court described the issue using broad language, it did not render a broad decision. Rather, the Court limited its decision to the facts of the case. First, the *Bell* Court decided that the reference which provided the amino acid sequence of the protein did not, by itself, make obvious the specifically claimed<sup>8</sup> correspondent gene because of the degeneracy of the genetic code. The Court then looked to the secondary reference to determine whether the cloning technique taught therein pointed the way to the gene. The Court reviewed the secondary reference and determined that it taught away from a

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<sup>8</sup>The claim in *Bell* covered a single particular sequence of the 10<sup>36</sup> sequences that could be theorized as coding for the protein. The claims before us cover all sequences which code for the protein.

viable process which could be used for cloning the particular gene set forth in the *Bell* application.<sup>9</sup>

Importantly, the Court did not dismiss or disparage the PTO's premise that knowledge of the amino acid sequence of a protein in conjunction with a reference indicating a general method of cloning can render the gene *prima facie* obvious.

In the case before us, appellants have admitted that the methodology of cDNA cloning set forth in the Maniatis reference and, indeed, the methodology utilized by the appellants and set forth in the instant specification is "conventional" and not the basis for the claimed invention. On this point the amendment submitted August 22, 1991 (page 11) states the following:

Maniatis is nothing more than a general text on cDNA cloning methodology. ... Such methodology is conventional and not the basis of the claimed invention. ... Applicant's invention in Claims 4-7 resides in unique sequences which not only are not taught by Maniatis, but also are different from the DNA sequences of the other references.

Appellants urge that the rejection before us is one based on "obviousness to try." We are unpersuaded by this argument. Facts which infer that one skilled in the art would be successful in isolating a gene using a certain cloning procedure,

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<sup>9</sup>The court decided that the reference cloning procedure required the protein to have amino acids which had unique codons, i.e., amino acids coded for by but one codon.

when unrebutted, may constitute sufficient factual inference to warrant the ultimate legal conclusion of obviousness, even when use of the isolation procedure constitutes "trying." See *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). In this case, appellants have provided no evidence whatsoever that one skilled in the art, following the technique of the Maniatis reference, would have had any difficulty isolating the gene of interest or would have been able to clone the gene only by undue experimentation.<sup>10</sup>

We hold that under the facts presented in this appeal, a *prima facie* case of obviousness has been established by a reference teaching the isolation and partial sequencing of a protein in combination with a reference indicating a general method of cloning. The *prima facie* case is based on factual inferences and is rebuttable.

We do not lightly dismiss appellants' argument that the examiner has not given sufficient weight to the structure or form of the compound or composition, and has improperly concentrated on the method of making it. We recognize that in *Amgen, supra*, the Federal Circuit questioned the focus of the District Court

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<sup>10</sup>We are aware that the Bohlen reference describes only a partial sequence of the protein. Appellants have not challenged the Bohlen reference on this basis. We note that appellants' sequencing of the protein was to the extent of the same partial sequence.

and the parties on the obviousness of the process of isolating the gene when the claims were directed to the products themselves (genes). 927 F.2d at 1207, 18 USPQ2d at 1022. We are also aware that in *In re Bell, supra*, the Federal Circuit indicated that the PTO's focus on the method of isolating the clone was misplaced because the issue was "the obviousness of the claimed compositions, not of the method by which they are made." 991 F.2d at 785, 26 USPQ2d at 1532.

We recognize that the evidence presented in the *Amgen* cases and some statements in textbooks indicate the truth of the adage, "Many things happen between the cup and the lip." We realize that "textbook" procedures may not always work as predicted. On this point, Watson et al. in a different text, Molecular Biology of the Gene, Fourth Edition, Benjamin/Cummings Publishing Co., p. 611, 1987, make the following comment:

If, however, the proteins of interest have been characterized by partial or full amino acid sequencing, then an important shortcut may be used. Given an amino acid sequence, intelligent guesses can be made as to its corresponding mRNA (DNA) sequence. Because all amino acids but one are specified by more than one codon (Chapter 15), it is not possible to go from an amino acid sequence to a DNA sequence unambiguously. By focusing, however, on sequences that mainly contain the less common amino acids, it is usually possible to define a small collection of oligonucleotides, one of which should be exactly complementary to the segment of interest (Figure 19-18). Such a restricted collection can then be used as probes to

identify the complementary cDNA clones by hybridization." Already this approach has been used to isolate a number of important cDNA clones, and while it never is as simple as described here, it nevertheless is a practical technique that is bound to be increasingly employed. (emphasis added)

In the case before us, appellants have not challenged the examiner's assertion that the probing procedure set forth by Maniatis would have isolated the gene without undue experimentation. Indeed, probing appears to have become so routine that appellants' specification leaves the reader to determine the probing technique used and says nothing about the initial probe and probing technique used by appellants to isolate the bovine DNA. As we view it, the suggestions in the prior art references cited by the examiner would have given rise to a reasonable expectation of success. Absolute certainty is not the criterion.

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"In this case the ability of the hybridization phenomenon to differentiate among the numerous genes and isolate the desired gene, is what distinguishes a "factual inference" from the "obvious to try" approach discouraged by the court in *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966). In *Tomlinson*, the Patent Office was of the opinion that it was obvious to determine which stabilizers for other materials known in the art would and which would not stabilize polypropylene. However, there was no way to predetermine which stabilizers were effective other than to produce the claimed composition. In this case, however, there is a way to preselect and isolate the gene which will produce the protein. Preselection is accomplished via a routine hybridization procedure.

Appellants note that the claimed DNA was isolated from bovine uterus and human placenta tissues whereas the prior art references isolated the protein from rat brain and bovine brain tissues. Appellants urge that there is nothing in the teachings of the references which suggests the use of bovine uterus or human placenta tissues as a source of the DNA. We are unpersuaded by this argument. We agree with appellants that both Rauvala and Bohlen teach that the protein is tissue specific, i.e., brain specific. Nevertheless, the claims before us are directed to the product and not the method of isolation. Appellants have not shown that the claimed DNA was not present in and could not have been readily isolated from the brain tissue utilized by Bohlen. Appellants have noticed a difference in the tissue source of the DNA but have not effectively tied this difference and their use of uterus and placenta tissue into a viable inoperability argument vis-à-vis the prior art's teaching that the protein was brain specific.

Appellants urge that the claims directed to the human DNA are patentably distinct over those to bovine DNA because the Bohlen protein teachings are limited to bovine sequences. However, Bohlen clearly teaches that the N-terminal amino acid sequences of human and bovine heparin binding factor are essentially the same and that the protein is highly conserved between species. One of ordinary skill in the art, having

isolated the bovine DNA, would have expected conservation between species, and would normally have used the bovine DNA as a probe for human DNA. This is standard practice in the art and has not been denied by appellants.

We consider next the rejection over Rauvala in view of Maniatis. We reverse this rejection because there is nothing in the Rauvala reference which teaches that the rat protein or the DNA coding for the rat protein are sufficiently homologous to the bovine and human versions that a rat DNA could be used as a successful probe. On this point see *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) wherein the court said:

While this testimony indicates that it might have been feasible, perhaps obvious to try, to successfully probe a human cDNA library with a monkey cDNA probe, it does not indicate that the gene could have been identified and isolated with a reasonable likelihood of success. Neither the DNA nucleotide sequence of the human EPO gene nor its exact degree of homology with the monkey EPO gene was known at the time.


The burden is upon the examiner to establish a *prima facie* case. In this instance, the *prima facie* case requires proof of known and sufficient homology between species to show a reasonable expectation of success in carrying out the probing work. That teaching can not come from the patent applicant's specification.

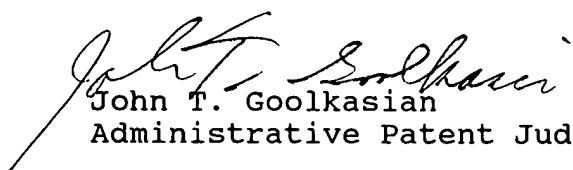
Appeal No. 92-3627

The examiner's rejection of claims 4 through 7 under 35 U.S.C. § 103 is affirmed with regard to the rejection of Bohlen in view of Maniatis but reversed with regard to Rauvala in view of Maniatis.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a). See the final rule notice, 54 F.R. 29548 (July 13, 1989), 1105 O.G. 5 (August 1, 1989).

**AFFIRMED**

  
Melvin Goldstein )  
Administrative Patent Judge)

  
John T. Goolkasian )  
Administrative Patent Judge)

  
William F. Smith )  
Administrative Patent Judge)

BOARD OF PATENT  
APPEALS  
AND  
INTERFERENCES

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APPENDIX

4. A purified and isolated DNA sequence consisting of a sequence encoding human heparin binding growth factor of 168 amino acids having the following amino acid sequence:

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|---|-----|
| Met Gln Ala Gln Gln Tyr Gln Gln Gln Arg Arg Lys Phe Ala Ala | 15  |
| Ala Phe Leu Ala Phe Ile Phe Ile Leu Ala Ala Val Asp The Ala | 30  |
| Glu Ala Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser | 45  |
| Asp Cys Gly Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly | 60  |
| Asp Cys Gly Leu Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu | 75  |
| Cys Lys Gln Thr Met Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn | 90  |
| Trp Lys Lys Gln Phe Gly Ala Glu Cys Lys Tyr Gln Phe Gln Ala | 105 |
| Trp Gly Glu Cys Asp Leu Asn Thr Ala Leu Lys Thr Arg Thr Gly | 120 |
| Ser Leu Lys Arg Ala Leu His Asn Ala Glu Cys Gln Lys Thr Val | 135 |
| Thr Ile Ser Lys Pro Cys Gly Lys Leu Thr Lys Pro Lys Pro Gln | 150 |
| Ala Glu Ser Lys Lys Lys Lys Lys Glu Gly Lys Lys Gln Glu Lys | 165 |
| Met Leu Asp   | 168 |